amendments and remarks herein address the considerations discussed during the interview.

Rejections Under 35 U.S.C. § 112, First Paragraph

Applicants respectfully traverse the rejection of claims 17-39, under 35 U.S.C. § 112, first paragraph, as allegedly not commensurate in scope with the enablement provided in the specification. Applicants respectfully disagree with the position taken in the Office Action that implanted β cells would be prevented from ameliorating or forestalling a clinical symptom of diabetes by autoreactive T cells. Applicants respectfully submit that the claims recite the term "implanting," which is defined on page 14, lines 6-11, of the specification to mean "the introduction or transplantation of cells into an individual wherein the cells remain viable after implantation and maintain their glucose-regulated insulin secretion for at least one stimulation of glucose uptake." Therefore, the claims are distinct from methods where T-cells prevent implanted β cells from secreting sufficient insulin for at least one stimulation of glucose uptake.

Furthermore, Applicants respectfully disagree with the position taken in the Office Action that the teaching and guidance provided in the specification for administering immunosuppressive agents or masking surface molecules is directed to unclaimed limitations. The teaching and guidance to which Applicants pointed in the previous response, although not

specifically recited the claims, falls within the scope of the claims. Furthermore, it is the function of the specification, and not necessarily the claims, to describe the invention in such terms that inform those skilled in the art how to make and use the claimed invention. Therefore, Applicants maintain that the claims are sufficiently enabled by the teaching and guidance provided in the specification as set forth previously.

Applicants maintain that the term proinsulin as it is used in the claims and defined in the specification is consistent with the normal usage of the term in the art. Nevertheless, in order to further prosecution of this application, the claims have been amended to replace the term proinsulin with the term insulin precursor.

Applicant maintains that use of a glucose-regulated protease capable of cleaving the proinsulin cleavage site of an insulin precursor to produce insulin in the claimed methods is sufficiently enabled by the specification. As set forth previously, the specification teaches that insulin can be produced from an insulin precursor having naturally occurring cleavage sites or modified insulin precursor having cleavage sites modified to a cognate recognition site for a desired protease. Several proteases and their cognate recognition sites are taught in the specification or well known in the art. In view of the teaching and guidance provided in the specification those skilled in the art would have been able to readily modify insulin to include a modified protease site using routine methods. Furthermore, coexpression of the modified insulin with

the cognate protease as claimed and taught in the specification would have resulted in cleavage of the modified insulin precursor to produce insulin as claimed.

Regarding the position in the Office Action that the teaching and guidance provided in the specification for the use of the PC2 protease in the claimed methods is directed to unclaimed limitations, Applicants maintain, for the reasons set forth above in regard to immunosupression, that the guidance is relevant for demonstrating enablement because it falls within the scope of the claims, whether or not the claims are limited to the PC2 embodiment.

Applicants respectfully disagree with the position taken in the Office Action that the use of the PC2 enzyme to produce mature insulin in the claimed methods was not adequately described in the specification. The specification teaches that PC2 is an example of a protease that can be used in the invention (see page 37, lines 26-28). The specification further teaches that when proteases that do not recognize a native proinsulin cleavage site are used, the proinsulin cleavage site can be modified to the cognate recognition site for the protease so that the site can be cleaved by the protease (see page 37, line 32, through page 38, line 4). Furthermore, the description in Smeekins et al. that the PC2 enzyme is highly selective for the C-peptide-A-chain junction of rat proinsulin I, referred to in Applicant's previous response, demonstrates that it was well known in the art that the PC2 enzyme is capable of cleaving the C-peptide-A-chain junction of rat proinsulin I. Thus, the

specification, in view of that which was known in the art, adequately describes use of the PC2 enzyme to produce mature insulin in the claimed methods.

For the reasons set forth above, the use of the PC2 enzyme to produce mature insulin falls within the scope of the claims and is adequately described by the specification. Accordingly, Applicants' maintain that the specification is sufficiently enabling for use of a proinsulin cleavage site in an insulin precursor as demonstrated, for example, by the teaching and guidance for use of the PC2 enzyme to produce mature insulin as set forth previously. Therefore, reconsideration and withdrawal of the rejection of claims 17-39, under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Applicants respectfully traverse the rejection of claims 28-30 and 32-39, under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which is not adequately described in the specification. Applicant respectfully disagrees with the assertion in the Office Action that Applicant's description of an intermediate product is insufficient description of the enzyme responsible for the formulation of said product. The specification describes the intermediates of the hexosamine biosynthetic pathway in the context of a well known pathway. As set forth previously, the specification identifies fructose-6-phosphate, glucosamine-6-phosphate, glucosamine, N-acetyl glucosamine-6-phosphate, N-acetyl glucosamine-1-phosphate and UDP-N-acetyl glucosamine in the context of the hexosamine biosynthetic pathway (see, for example, page 19, lines 5-13 and page 21, lines 10-18). The relationship of these intermediates

to each other in the hexosamine biosynthetic pathway was well known in the art as demonstrated, for example, by Figure 1 of McClain et al., Diabetes 45:1003-1009 (1996), attached hereto as Exhibit A. More specifically, Figure 1 of McClain et al. shows the series of reactions in the hexosamine biosynthetic pathway including conversion of fructose-6-phosphate to glucosamine-6-phosphate, conversion of glucosamine-6-phosphate to N-acetyl glucosamine-6-phosphate, conversion of N-acetyl glucosamine-6-phosphate to N-acetyl glucosamine-1-phosphate, and conversion of N-acetyl glucosamine-1-phosphate to UDP-N-acetyl glucosamine.

Furthermore, those skilled in the art would have known or been able to identify a hexosamine biosynthetic pathway enzyme capable of the above-identified hexosamine biosynthetic pathway reactions. In particular, SWISS-PROT entry P43577, attached herewith as Exhibit B, indicates that glucosamine-phosphate N-acetyl transferase (EC 2.3.1.4) was known to convert glucosamine-6-phosphate to N-acetyl glucosamine-6-phosphate (see page 2, under the headings "catalytic activity" and "pathway"). Moreover, as described on page 1 of Exhibit B, the sequence of the protein was entered in SWISS-PROT in November 1995 and was, therefore, known prior to the time of filing. As demonstrated by SWISS-PROT entry P38628, attached herewith as Exhibit C, Phosphoacetylglucosamine mutase (EC 5.4.2.3) was known to convert N-acetyl glucosamine-6-phosphate to N-acetyl glucosamine-1-phosphate and the sequence was entered in SWISS-PROT in October 1995, prior to the time of filing. The enzyme UDP-N-acetyl glucosamine pyrophosphorylase (EC 2.7.7.23) was known to convert N-acetyl glucosamine-1-phosphate to UDP-N-acetyl glucosamine and its sequence was known prior to the time of filing, as shown in

SWISS-PROT entry P43123, attached herewith as Exhibit D. Because those skilled in the art would have known of or been able to identify enzymes capable of performing the reactions of the hexosamine biosynthetic pathway described in the specification, they would have understood that applicants were in possession of the hexosamine biosynthetic enzymes recited in the claims. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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APPENDIX A

A marked up version of the amended claims to show changes made is provided below. Text to be added is underlined and text to be deleted is in brackets.

17. (Amended) A method of treating diabetes or forestalling a clinical symptom indicative of diabetes comprising implanting into an individual cells coexpressing an insulin precursor [proinsulin] containing a proinsulin cleavage site and a glucose-regulated protease capable of cleaving said proinsulin cleavage site to produce insulin.

28. (Amended) A method of treating diabetes or forestalling a clinical symptom indicative of diabetes comprising implanting into an individual cells coexpressing an insulin precursor [proinsulin] containing a proinsulin cleavage site, a glucose-regulated protease capable of cleaving said proinsulin cleavage site to produce insulin, and a hexosamine biosynthetic pathway enzyme.